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T1 mapping in ischaemic heart disease

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A unique feature of cardiac magnetic resonance is its ability to characterize myocardium. Proton relaxation times, T1, T2, and T2* are a reflection of the composition of individual tissues, and change in the presence of disease. Research into T1 mapping has largely been focused in the study of cardiomyopathies, but T1 mapping also shows huge potential in the study of ischaemic heart disease. In fact, the first cardiac T1 maps were used to characterize myocardial infarction. Robust high-resolution myocardial T1 mapping is now available for use as a clinical tool. This quantitative technique is simple to perform and analyse, minimally subjective, and highly reproducible. This review aims to summarize the present state of research on the topic, and to show the clinical potential of this method to aid the diagnosis and treatment of patients with ischaemic heart disease.

Keywords T1 Mapping • ECV • Myocardial ischaemia • Myocardial infarction • Ischaemic heart disease

Introduction

Cardiac magnetic resonance (CMR) imaging is the gold standard imaging technique for cardiac anatomy and function. A unique feature of CMR is its ability to characterize tissue using proton relaxation times, T1, T2, and T2*. These values are largely dependent on the physical and chemical environments of water protons in tissue. Using conventional CMR techniques, higher signal intensity with either T1 weighted sequences using gadolinium contrast agents or T2 weighted techniques can detect myocardial infarction (MI) or focal oedema, respectively. However, signal intensity in CMR images is displayed on an arbitrary scale. Therefore, signals cannot be quantified or compared between subjects or follow-up examinations in individuals. Visualization of pathology depends on a contrast existing between 'normal' and 'abnormal' myocardium.

T1 values are a reflection of the composition of individual tissues, with each tissue type having a normal intrinsic value. This value changes in the presence of disease, and therefore can be used to study and diagnose tissue pathology.¹ T1 reflects the mobility of nuclei (predominantly protons) and how they are bound within macromolecules. Therefore, it can be used to study macromolecular content, water binding, and water content. Muscle has an intermediate value but with inflammation, water content increases and is matched by an increase in T1.

When T1 is measured on a pixel-by-pixel basis, the resulting T1 values can be visualized as a T1 map. In this map, the signal intensity

of each pixel reflects the absolute T1 value of the underlying voxel. T1 weighted sequences provide the basis for late gadolinium enhancement (LGE) imaging that is now universally used in the detection of MI and focal lesions of myocarditis and other diseases. The interest in absolute quantification of T1 values in a clinical setting has risen recently. Over the last few years, a number of sequences have been developed which allow robust high-resolution T1 mapping.^{2,3}

History

T1 quantification has been the basis for diagnostic methods since the beginning of magnetic resonance imaging in the early 1970s. This was initially driven by the finding that cancerous tissue could be differentiated on the basis of abnormal T1.⁴ The earliest studies looking at changes in T1 in the heart were performed *in vitro* using samples from dog hearts.⁵ These showed that T1 increased with ischaemia, and that the magnitude of increase was related to the duration and severity of ischaemia. *In vivo* studies then demonstrated increases in T1 and T2 with infarction. The first studies to quantify myocardial T1 in humans with recent MI also detected increased T1 and were the first to present their findings as a map of the T1 values of the heart.⁶ T1 was found to increase within the first hour of ischaemia,⁷ reach its peak in patients with STEMI between days 8 and 14, before gradually returning to baseline.⁸

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Following these early studies, specific techniques were developed to exploit these changes in tissue oedema. The short-inversion-time inversion-recovery (STIR) magnetic resonance imaging pulse sequence, which generates high contrast from both T1 and T2 prolongation in the presence of water, is now widely used in the detection of myocardial oedema in myocarditis⁹ and acute MI (Figure 1).¹⁰

Ex vivo measurements of T1 are usually based on inversion-recovery sequences, requiring an interval of at least five times the T1 to allow for adequate recovery. This technique was used in the initial studies,^{6,8} as at the very low field strengths (0.08 T), T1 is short (305 ms) and acquisition schemes can easily be fitted into the cardiac cycle. As field strength increases to 1.5 T, myocardial T1 increases to ~1000 ms, which exceeds cardiac cycle length in most patients. As a consequence, conventional acquisition schemes in these situations cannot be confined to single cardiac cycles and require long acquisition times. This prevents their use as breath hold techniques in clinical routine.

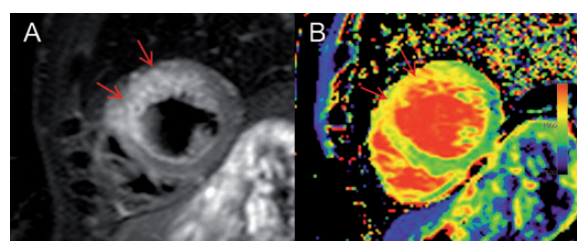


Figure 1: (A) Short-axis STIR image in 52-year-old male 6 days post-anterior STEMI with localized hyperintensity indicating acute oedema (arrows). (B) Corresponding Native T1 map demonstrates a similar area of injury; however, there is a zone with a range of increased T1 (arrows) reflecting the increasing severity of injury from epicardium to endocardium.

T1 quantification in ischaemic heart disease can be divided into native and post-contrast applications. Native T1 values in this setting are a reflection of the composite water signal from interstitium and myocytes, and therefore reflect changes in myocardial water content. As standard gadolinium contrast agents are extravascular and extracellular, changes in T1 following contrast administration reflect gadolinium concentration in the extravascular compartment. These changes can then be used to estimate extracellular volume (ECV). To summarize, native T1 detects both intracellular and extracellular changes whereas ECV estimates changes in the myocardial interstitium (Figure 2).

Native myocardial applications

Myocardial oedema

Ischaemic cell death is characterized by cellular oedema.¹¹ In normal myocardium, water balance is tightly regulated by cell membrane function, starling filtration, and lymphatic drainage. Intracellular water accounts for 79% of total water or about 380 mL/100 g of dry tissue and varies little between individuals or species.¹² The first studies looking at T1 values in myocardial ischaemia came from the knowledge that ischaemia results in oedema.¹³ In fact, the amount of water present after reflow has been shown to correlate with myocardial survival in an animal model.¹⁴

Cellular oedema occurs within 15 min of coronary occlusion.¹⁵ Myocardial water reaches its peak in the first 1–2 h after onset of ischaemia¹⁶ and is caused by dysfunction of the complex processes that regulate myocardial water balance. The alterations in cell membrane function can be simplified into three stages.¹⁷ Initially, there is inhibition of the Na⁺/K⁺ pump, resulting in an influx of water as it follows the increased intracellular Na⁺. The second stage involves sarcolemmal transport systems, again allowing intracellular water to increase. The final stage is of physical disruption of the cell membrane, with an equilibrium forming between the interior and exterior of the cell.

Reperfusion can worsen oedema and is predominantly determined by the duration and severity of ischaemia.¹⁸ The main

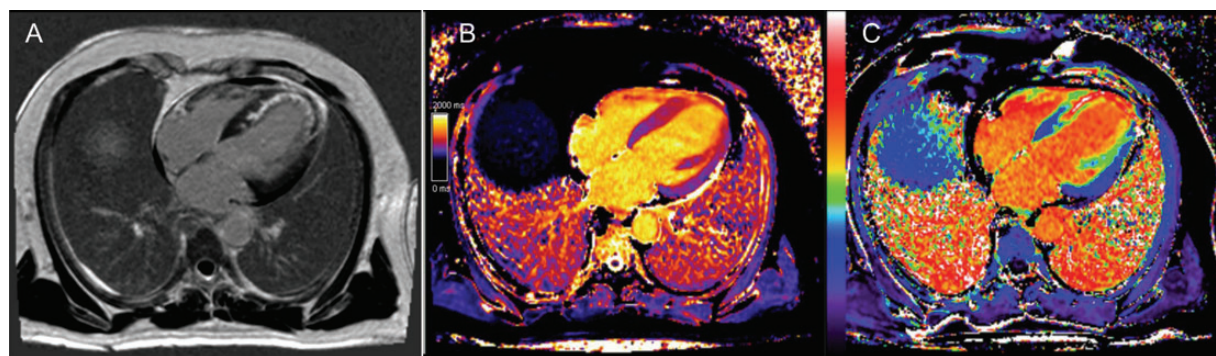


Figure 2: Images from a patient with recent acute MI resulting from left anterior descending artery occlusion. (A) LGE imaging demonstrating apical and apico-septal subendocardial MI. (B) Native T1 map with increased T1 in the apex and apical septum. (C) Post-gadolinium contrast ECV map shows a range of myocardial injury, the most severe injury being subendocardial. The range of injury in the ECV map can be compared with the binary infarcted/not-infarcted information in the LGE image. Images courtesy of Martin Ugander MD PhD and Peder Sörensson MD PhD, Karolinska Institutet, Stockholm, Sweden in collaboration with Peter Kellman PhD, National Institutes of Health, Bethesda, MD, USA.

mechanisms are hyperaemia and osmotic changes. Following restoration of arterial flow to ischaemic myocardium blood flow greatly increases. There is a localized increase in cellular osmolality as high energy phosphates and macromolecules are broken down.¹⁹ Despite the diffusion of these products into extracellular spaces, intracellular osmolality increases.¹⁹ On reperfusion, the hyperosmolar myocardial cells absorb extra fluid across this osmotic gradient.

T1 changes in myocardial infarction

The oedema in myocardial ischaemia and infarction can be detected by increases in T1. T1 can detect acute MI with a high sensitivity and specificity.^{20–22} The cut-off T1 value that demarcates infarcted myocardium from the surrounding oedematous myocardium remains to be delineated; however, previous studies have demonstrated high accuracy using three²⁰ and two²¹ standard deviations above mean values. Whereas most studies have focused on patients with STEMI, T1 mapping can also identify infarction in patients with non-STEMI.²¹ There is a progression in T1 from normal to that of maximal injury, a finding similar to the peri-infarct zone described in studies studying MI with contrast agents.²³ In acute MI, T1 increases are more pronounced in myocardium that will become infarcted than in myocardium which will be salvaged by reperfusion.²⁴ Following reperfusion, T1 increases further in infarcted tissue, but remains unchanged in salvaged myocardium.

Elevated water content also increases T2. T2 weighted imaging has been used for oedema imaging since the first papers demonstrating T2 prolongation in MI in dogs²⁵ and humans.²⁶ A difficulty with this technique is the need for signal uniformity as the increase in T2 associated with oedema in acute MI is relatively small—in the order of 15–20 ms.⁷ The STIR sequence, a technique which uses changes in both T1 and T2 to obtain contrast, is commonly used to identify areas of hyperintense signal. However, a number of technical issues may affect the signal intensity, including choice of coil used, artefacts from slow flowing blood, slice thickness, and TR.²⁷ As absolute values are not quantified, contrast depends on the presence of 'normal' myocardium. Therefore, diseases that involve diffuse or widespread disease of the myocardium cannot be identified. T2 mapping may overcome some of these limitations.²⁸

Native T1 measurement may have some other novel uses. For example, methemoglobin, formed from thrombus, has a T1 shortening effect.²⁹ This can detect intramyocardial haemorrhage in MI,³⁰ a marker of adverse cardiac outcomes.

Duration of T1 changes

After restoration of normal myocardial blood flow following a brief period of ischaemia, the ECG can normalize within seconds and functional changes normalize within 5 min. However, increased intracellular water is present for a much greater period of time. Pathological studies demonstrate a gradual resolution of intracellular oedema, typically over 1 month.³¹ These findings were matched in an early study which demonstrated that water content was elevated with corresponding prolongation of T1 in dogs 3 weeks following MI.⁷ A T1 mapping study demonstrated increased T1 for up to 2 months after MI.²² Using the STIR technique, persistent small areas of hyperintensity have been noted up to 6 months after infarction.¹⁰ Potential reasons for persistent oedema include increased wall stress and/or

residual/recurring ischaemia, alterations in drainage of the infarcted segments or continuing tissue repair.

Post-contrast applications

T1 mapping in acute myocardial infarction

Gadolinium contrast administration shortens myocardial T1. The volume of distribution for contrast agents is greater in areas of cell membrane rupture, such as infarction. The increased volume of distribution for gadolinium agents in infarction shortens the T1 of infarcted areas to a greater extent than that of normal myocardium. The difference in T1 can be used to distinguish between normal and infarcted tissue. This property, used in a non-quantitative manner in LGE imaging, is the *in vivo* gold standard method of detecting MI. In acutely injured myocardium, the higher initial concentration of free water and therefore elevated native T1 will reduce the net change in T1 and thus reduce the effective T1-shortening and apparent contrast enhancement.²⁰

Chronic myocardial infarction

In chronic MI, there is replacement of myocardial cells by scarring or fibrosis with an increase in extracellular collagen. Importantly, there is no oedema, as this has resolved in the initial weeks after MI. Therefore, T1 values are higher than in normal myocardium, but not as high as in acute MI.²⁰ In some areas of chronic MI areas of lipomatous metaplasia can be seen, particularly when T1 weighted sequences are used.³² As fat has a T1 value much lower than myocardium (230–350 ms), T1 mapping can be used to identify intramyocardial fat.³³

Microvascular obstruction

Native T1 values of areas of microvascular obstruction (MVO) have been found to be slightly higher than that of remote myocardium, but lower than the surrounding hyperenhanced area.^{20,21} This may be due to reduced blood supply in this area, which limits oedema. Whereas MI detection using LGE reflects decreased wash-out of contrast, areas of MVO can be detected by decreased wash-in. Gadolinium will, therefore, have less T1 shortening action in areas of MVO if T1 times are measured early after contrast administration.

Area at risk

The area at risk (AAR) refers to the hypoperfused myocardium during coronary occlusion.³⁴ In revascularized myocardium, the relation between the AAR and the infarct allows us to quantify the volume of myocardium that reperfusion successfully salvaged from ischaemic death. The AAR can therefore not only be used as a measure of the severity of ischaemic insult, it could also be used to measure the efficacy of a treatment. To study these changes, the AAR must be clearly identified. The unique tissue characterization abilities of CMR make it a suitable method for identifying the AAR.³⁵

The basis of the identification of the AAR is similar for both T1 mapping and T2 weighted imaging, i.e. protons from increased water in oedematous myocardium caused by ischaemia are detectable by increases in T1 and T2. It has been known for many years that T1 weighted imaging *ex vivo* was able to delineate the AAR.³⁶ These findings were recently confirmed *in vivo*, where the AAR

defined by microspheres closely matched the AAR defined by increased T1.³⁷ In keeping with the concept of oedema being a marker of severity of injury, T1 changes can predict myocardial salvage. It has been found that T1 is higher in myocardium that ultimately goes on to undergo infarction than in salvaged myocardium.²⁴ Mapping techniques, using T1 or T2, have the potential to improve the objectivity of the AAR imaging.

Extracellular volume

The myocardium is made up of both myocardial cells and their surrounding interstitium. The ECV can increase in myocardial disease, especially through processes that lead to an accumulation of collagen. The increase can be diffuse or focal as in the case of infarction. The gold standard test, myocardial biopsy, has both significant morbidity and sampling error. T1 mapping can be used to quantify ECV, providing a non-invasive alternative method of quantifying fibrosis. Extracellular volume not only provides a physiologically intuitive unit of measurement, increased ECV is strongly associated with adverse outcomes.³⁸

Post-contrast T1 values alone could be used to estimate the ECV; however, there are multiple factors that influence post-contrast myocardial T1. By normalizing myocardial T1 in relation to blood T1, these factors are minimized. The ECV is calculated using the change in T1 values in myocardium and blood with contrast, and the haematocrit. Increased ECV has been found not only in diffuse myocardial diseases such as aortic stenosis and hypertrophic cardiomyopathy,³⁹ but also in ischaemic heart disease. In acutely infarcted myocardium, ECV is increased as a result of cellular breakdown. In chronic infarction, ECV remains elevated due to the development of replacement fibrosis. Extracellular volume increases in line with increasing levels of myocardial damage. It has been shown that the ECV of infarcted myocardium is higher than the ECV in other diseases causing myocardial fibrosis.⁴⁰

The ECV can be abnormal even in normal appearing myocardium in patients with ischaemic cardiomyopathy.⁴¹ Extracellular volume increases with worsening left ventricular function. This correlates with pathological findings from explanted hearts of patients with ischaemic cardiomyopathy,⁴² in which interstitial fibrosis in areas remote from infarction was increased over two-fold in comparison with controls. Raised ECV has now been found to be a marker of adverse short-term outcomes in a wide range of patients.³⁸

It can be shown that the ECV of salvaged myocardium is higher than that of the remote myocardium as a result of extracellular oedema. Extracellular volume can delineate the AAR from infarcted and normal myocardium.⁴³ The post-contrast T1 in the AAR signal intensity differs less than 2SD from the remote myocardium (~50 ms), and is therefore difficult to detect using LGE alone. The combination of native and post-contrast images demonstrates that the ECV in the AAR is significantly elevated from remote myocardium.

Technical aspects

T1 mapping uses multiple scans with varying degree of signal recovery in order to calculate T1 values on a pixel-by-pixel basis, from which a parametric image can be reconstructed. Pixel intensities in these images correspond to T1 values. This can then be presented as a grey-scale or colour map of the myocardium.

To produce raw data with varying degree of signal recovery, most T1 mapping pulse sequences acquire images at different delay time following a 180° or 90° prepulse (inversion recovery or saturation recovery, respectively). Inversion pulses can only be used when the signal has sufficiently recovered from all preceding experiments. In order to avoid long waiting times, clinical inversion recovery-based techniques (e.g. modified Look–Locker inversion recovery, MOLLI²) are based on the method that was introduced by Look and Locker⁴⁴ and acquire data at multiple time points following one inversion pulse. Inversion pulses provide higher dynamic range than saturation pulses, but the necessity to use multiple-readout schemes introduces a certain degree of heart rate dependence, which becomes relevant at high flip angles (>35° in balanced steady-state free precession) and high heart rates (>100 bpm²⁰). Saturation pulses provide lower dynamic range to start with but, when carried out separately for each raw image, allow for using high flip angles (e.g. 70°) without heart rate dependence.⁴⁵ As a result, both approaches exhibit different levels of accuracy and precision. An in-depth discussion of technical aspects and on-going technical development is beyond the scope of this manuscript but can be found in the consensus document on myocardial T1 mapping and ECV quantification by the T1 Mapping Development Group.⁴⁶

Technical factors affecting T1

Factors that influence T1 itself include cardiac phase and field strength.⁴⁶ The measured T1 value will reflect the T1 of blood in the myocardium in addition to that of the myocardium. As myocardial blood flow occurs primarily during diastole, the phase in which the T1 is measured, systole or diastole, affects T1 measurement. Pre-contrast, arterial blood T1 is higher than that of myocardium, resulting in higher T1 in diastole than systole.⁴⁷

Only minor differences (a maximum of 2%) have been noted in the measurement of native T1 between the septal and non-septal regions.⁴⁷ No difference, however, has been found between basal, mid, and apical regions.⁴⁸

The relatively thin walls of the right ventricle are technically challenging to assess; however as spatial resolution improves, T1 mapping could also identify right ventricular injury.

Future potential of T1 mapping in ischaemic heart disease

T1 mapping provides a quantitative method to complement both oedema imaging (e.g. STIR) and infarct imaging (LGE). An advantage of T1 mapping is that by using a quantitative technique, both intra- and interobserver agreement are very high.^{47,48}

The data provided by native and post-contrast T1 mapping could help in the diagnosis of patients with acute chest pain, distinguishing acute coronary syndromes from myocarditis and Takotsubo cardiomyopathy,⁴⁹ and acute from chronic infarction. Furthermore, ECV could aid in the differentiation of ischaemic and non-ischaemic heart disease in cases of uncertainty.⁴¹

There is considerable evidence that increased ECV is a final common pathway in many kinds of myocardial disease.⁴² Even in MI patients, myocardium that appears 'normal' on LGE imaging can have increased ECV. Not only does this impact on the mechanical

and electrical function of the heart,^{50,51} it can predict mortality and other adverse cardiac events.³⁸ Endomyocardial biopsy is the standard of reference for quantifying fibrosis, but is an invasive procedure and prone to sampling error. It is known that the development of diffuse fibrosis is influenced by neurohormonal factors including angiotensin-converting enzyme, angiotensin II, catecholamines, and aldosterone. Standard heart-failure treatments, beta-blockers and angiotensin-converting enzyme inhibitors, can reduce diffuse myocardial fibrosis.⁴¹ Extracellular volume has a low variability across scans, and could be a biomarker in clinical trials.⁵² Extracellular volume could non-invasively, serially, and quantitatively assess fibrosis in the non-infarcted myocardium as a potential endpoint for pharmacological intervention in heart failure, using small groups of patients, greatly reducing trial costs. Looking to the future, the use of CMR tissue characterization techniques in clinical trials as surrogate, mechanistic, and secondary endpoints may increase.

In chronic ischaemic heart disease, standardized T1 thresholds or ECV values could detect and automatically quantify MI. In addition, the injury could be analysed, looking for MVO and myocardial haemorrhage and studying the peri-infarct zone. This could help the prediction of cardiac events; for instance, some studies have found that MVO is a predictor of adverse outcomes. The peri-infarct zone is potentially important pathophysiological substrate for arrhythmias. Presumptively normal myocardium has been used in prior studies to differentiate the infarct core (e.g. more than three standard deviations) from the heterogeneous peri-infarct zone, containing viable myocardium (e.g. between two and three standard deviations). This border zone may provide a substrate for ventricular tachycardia and sudden cardiac death.²³ T1 mapping can identify this zone and potentially be used in the study of ventricular arrhythmia.

Several CMR techniques can be used in the evaluation of myocardial viability. T1 mapping provides an alternative to the most frequently used method using LGE percentage of transmural.⁵³ In this way, the percentage of infarction in each voxel can be calculated. This allows for automatic quantification of myocardial infarction with higher accuracy and lower variability than a simple infarcted/not-infarcted algorithm.

Coronary microembolization is a frequent complication during PCI. As LGE using semi-automated thresholding underestimates myocardial damage,⁵⁴ T1 mapping techniques could identify areas of reversible and irreversible injury with the aim of improving revascularization techniques. In the field of research, it offers a quantitative alternative to T2 weighted methods to measure the AAR from MI in NSTEMI and STEMI.

Conclusion

T1 quantification has a long history in the study of ischaemic heart disease. Recent image sequence developments allow T1 values to be quickly and reproducibly quantified on a pixelwise basis and presented as T1 maps using clinical MR systems. Oedema from acute myocardial ischaemia and replacement fibrosis in chronic MI can be accurately detected and quantified. The combination of native and post-contrast images can detect not only MI and the AAR, but also demonstrate a range of myocardial injury by measuring ECV.

The precise role of T1 mapping in the evaluation of ischaemic heart disease remains to be defined, however its broad potential, and the

fact it is a quantitative measurement show much promise for the future.

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